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RESEARCH ARTICLE

4-CYANO-1,3-OXAZOLE-5-SULFONAMIDES AS NOVEL PROMISING ANTICANCER LEAD COMPOUNDS

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ABSTRACT

The available 2-acylamino-3,3-dichloroacrylonitriles when treated by sodium hydrogen sulfide undergo cyclization into the 4 cyano-1,3-oxazole-5-thioles. These latter compounds were converted into the 2-aryl-4-cyano-1,3-oxazole-5-sulfonamides using a standard reaction sequence. Synthesized compounds were screened for anticancer activity against a panel of 60 cancer cell lines at the National Cancer Institute, USA.

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INTRODUCTION

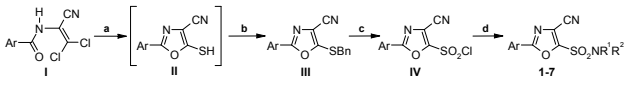
The ubiquitous oxazoles have attracted *increasing attention* in medicinal chemistry. The oxazole ring occurs naturally and the total synthesis of natural products with a wide variety of biological activities containing oxazole moieties is an area of intense research (Jin, 2016). Oxazoles have not only attracted great interest due to their appearance as subunit of various biologically active natural products, but also because of their utilities as valuable precursors in many useful synthetic transformations (Joshi *al.*, 2017; Ghani *et al.*, 2016). Oxazole derivatives are among the most useful heterocyclic compounds from both synthetic and medicinal chemistry aspects. Among the numerous heterocyclic moieties of biological and pharmacological interest, the oxazole framework represents an important structural motif in a number of biological activities, such as brain-derived neurotrophic factor induction (Maekawa *et al.*, 2003), trypanocidal activity (Pinto *et al.*, 1997), antifungus (Rawat *et al.*, 2016), anti-inflammation (Niraimathi *et al.*, 2011), antidepression and anticonvulsion (Song *et al.*, 2017), antimicrobial activity (Tomi *et al.*, 2015), and antidiabetes (Kumar *et al.*, 2008). Among oxazoles, the derivatives of 1,3-oxazoles play a fundamental role in the synthesis of numerous drugs such as anti-inflammatory (Abraham *et al.*, 2014), immunomodulatory (Mesaik *et al.*, 2004), antimalarial, antimicrobial, antiviral, and antifungal agents (Swellmeen, 2016; Sadek *et al.*, 2011). A number of studies have revealed their outstanding anticancer activities (Zhou *et al.*, 2016; El-Nezhawy *et al.*, 2016; Abd El-All *et al.*, 2015; Kumar *et al.*, 2010; Liu *et al.*, 2009; Maekawa *et al.*, 2003; Shriram *et al.*, 2013). We also have predicted by QSAR models and showed by experimental study that some 1,3-oxazole derivatives appear to inhibit some cancer cell lines (Semenyuta *et al.*, 2016). These observations prompted us to develop, synthesize, and evaluate a novel series of diverse chemical structures that include 1,3-oxazoles. A novel series of 4-cyano-1,3-oxazole-5-sulfonamide derivatives was synthesized. The synthesized compounds were tested for their

in vitro antitumor activity against a panel of 60 cancer cell lines at the National Cancer Institute, USA.

RESULTS AND DISCUSSION

Chemistry: Syntheses of compound 1-7 are depicted on Scheme 1. The available 2-aroylamino-3,3-dichloroacrylonitriles I were chosen as the starting materials (Drach *et al.*, 1974). By the action of an excess of sodium hydrogen sulfide they underwent cyclization into the substituted 5-mercaptooxazoles II (Vinogradova *et al.*, 1982).[24] The latter were immediately converted into the alkylation products III without isolation in the individual state. Oxidative chlorination of products III proceeds in aqueous acetic acid at 0°C to give 2-aryl-4-cyano-1,3-oxazole-5-sulfonyl chlorides IV with yields of 55–75%. The reactions of sulfonyl chlorides IV with piperidines and morpholine occur in a boiling anhydrous dioxane in the presence of triethylamine to give the sulfonamides 1-7 in yields of 65–75%. Structures of synthesized compounds were confirmed by the IR, ^{1}H and ^{13}C NMR, and GC-MS spectra. Chemical structures of synthesized compounds are shown in Table 1.

Scheme 1. Synthesis of 2-aryl-4-cyano-1,3-oxazole-5-sulfonamides 1-7[a]



[a]Reagents: (a) NaSH(excess), MeOH, 20-25°C, 24h; 5% hydrochloric acid; (b) benzyl chloride, Et_3N, MeOH, reflux, 2-3h; 20-25°C, 12h; (c) Cl_2, acetic acid, 0°C, 0.5h; 20-25°C, 12h; (d) piperidines or morpholine, Et_3N, reflux, 2h; 20-25°C, 12h, 65-75%.

Biological Evaluation

Primary Single High Dose (10^{-5} M) against Full NCI 60 Cells Panel *in Vitro* Assay

Results of the initial single dose (10 μM) testing of NSC 765529, NSC 765530, NSC 762255, NSC 762256, NSC 762257, NSC 762258 and NSC 762259 against the 60 cell lines of NCI are presented as o***ne dose*** mean graphs of the percent growth of the treated cells when compared to the untreated control cells in Figures 1-6. Activity of compounds is represented by the percentage of growth relative to untreated cells. The data summarized present a visual image consistent with results obtained from the NCI cancer screen. The individual response of each cell line to the agent is depicted by a bar graph extending either to the right or left of the mean, depending on whether the cell line was either more or less sensitive than the average response. The length of each bar is proportional to the relative sensitivity compared with the mean determination. The one dose mean graph representation of antitumor effects of NSC 765529 shows that colon, melanoma, and renal cell lines were particularly sensitive (Fig. 1).

The highest activity for this compound was 100% growth inhibition for the colon cancer cell line HCT-116, and the melanoma cancer cell line LOX IMVI followed by 98.8% growth inhibition for the renal cancer cell lines RXF 393 and A498 (Fig.1). A single dose of 10 μM of the test compound against the NCI 60 cell lines was used. Zero on the X-axis represents the mean percentage of growth of the tested cell lines. The percentage of growth of each cell line relative to the mean is represented by a horizontal bar extending to the right side indicating mre sensitivity or to the left side indicating less sensitivity. The one dose mean graph representation of antitumor effects of NSC 765530 in the *in vitro* cancer screen demonstrates that colon, melanoma, and renal cancer cell lines were also the most affected. The highest growth inhibition was found to be −100.0% growth for the HCT-116 cell line and –92.62% for COLO 205 (Fig. 2). The growth inhibition for the renal cancer cell lines RXF 393 and A498 was 95% followed by 89% growth inhibition for the melanoma cancer cell line LOX IMVI (Fig.2). The compound NSC 765530, as distinct from NSC 765529, also inhibited the growth of the ovarian cancer cell line OVCAR-3 by 94%.

The compound NSC 762255 exhibited pronounced cytotoxic effects in HCT-116 colon cancer (−75.4%), and NCI-H522 non-small cell lung cancer (−71.8%) cell lines (Fig.3). For NSC 762256, the highest growth inhibition was found to be –16.9% for the non-small cell lung cancer NCI-H522 cell line (Figure 4). For NSC 762257, the highest growth inhibition was found to be −66.8% for the non-small cell lung cancer NCI-H522, and −62.6% for colon cancer SW–620 cell lines (Figure 5). The compound NSC 76258 exhibited moderate cytotoxic effects only in NCI-H522 non-small cell lung cancer cell line (64.8%) (Fig. 6). NSC 762259 did not inhibit cancer cell lines studied (Data are not shown). After obtaining the results for the single dose assay, the tested compounds NSC 765529, NSC 765530, NSC 762255 and NSC 762257, which satisfied the predetermined threshold inhibition criteria of the NCI-60 one dose screening, were tested at five different concentrations (0.01, 0.1, 1, 10 and 100 μM) for each cell line (Tab. 1, Figs. 7-11). The outcomes were used to create log10 concentration versus percentage growth inhibition curves.

Three end points are used to determine compound activity. The GI50 value (growth inhibitory activity) corresponds to the concentration required to inhibit 50% of cells, the TGI value (cytostatic activity) is the concentration of the compound resulting in total growth inhibition, and LC50 value (cytotoxic activity) is the concentration of the compound required to kill 50% of cells at the end of the incubation period of 48 h. Fig. 7 shows pronounced cytotoxicity of the compounds NSC 765529, NSC 765530, NSC 762255 and NSC 762257, although with considerably divergent potencies against the individual cell lines. Screening profiles, as exemplified by Fig. 7, manifesting "differential" growth inhibition have been of particular interest as the basis for research applications of the screen, as well as for the selection and prioritization of compounds for *in vivo* evaluation.

The values (Molar) of GI_{50}, TGI and LC_{50} of the target compounds against the full 60-cell line panel are illustrated in Table 1. Figures 8 shows GI_{50}, TGI, and LC_{50} mean graphs for the compounds constructed from the data illustrated in Table 1, which are interpolated log10 values representing concentrations at which the percentage growth is +50, 0 and –50%, respectively. Each bar indicates whether the sensitivity of the cell line is greater (bar to the right) or less (bar to the left) than the average response. Both compounds NSC 765529 and NSC 765530 exhibited significant dose-dependent potent patterns of activity against most cancer cell lines.

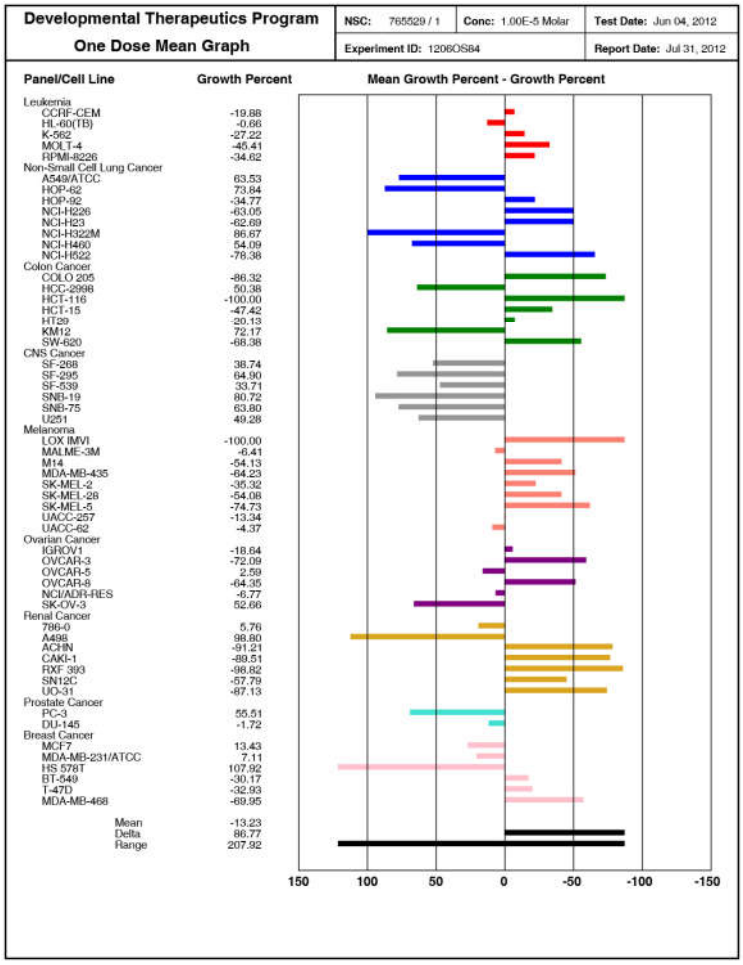


Figure 1. Sensitivity of the 60 human cancer cell lines to the cytotoxic activities of compound NSC 765529

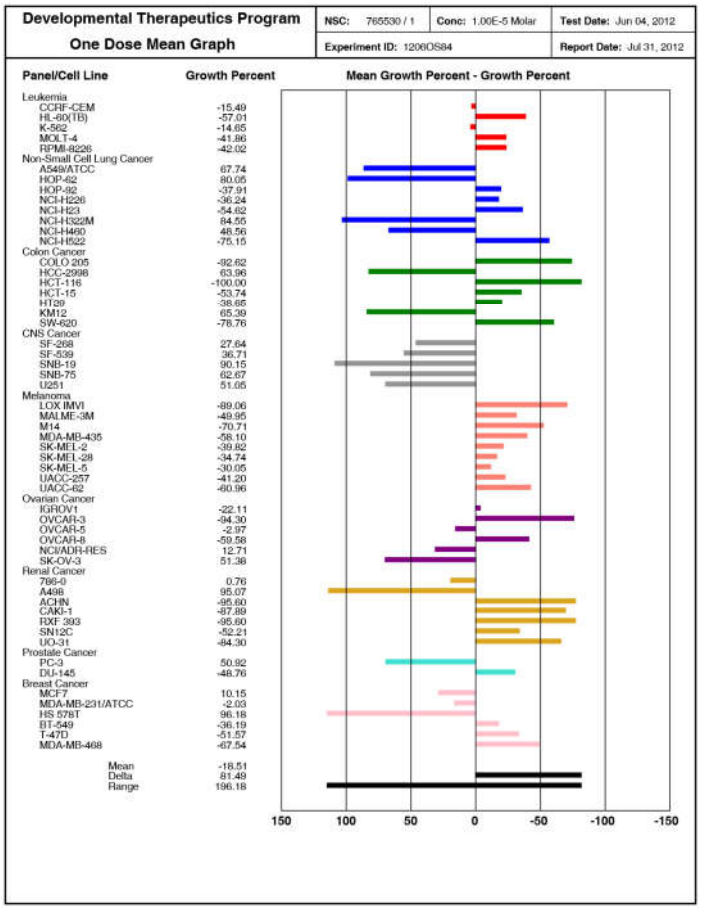


Figure 2. Sensitivity of the 60 human cancer cell lines to the cytotoxic activities of compound NSC 765530

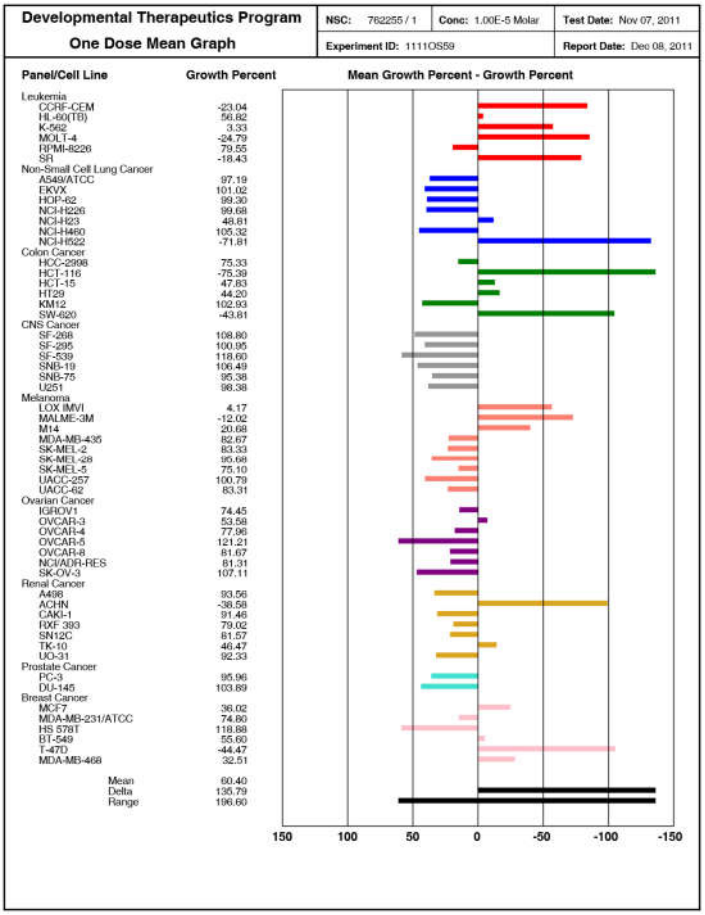


Figure 3. Sensitivity of the 60 human cancer cell lines to the cytotoxic activities of compound NSC 762255

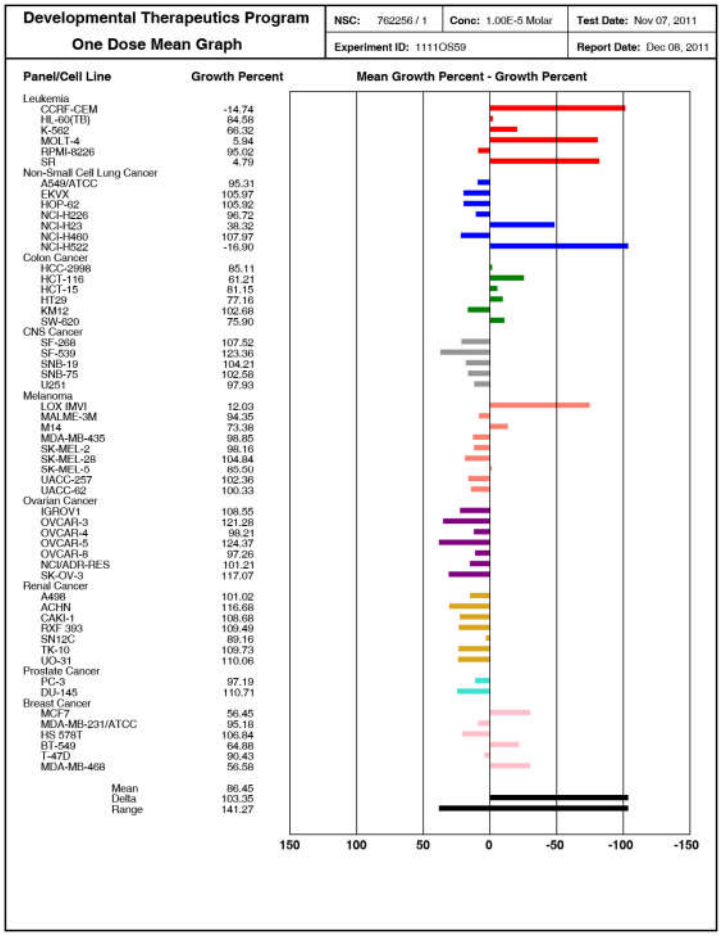


Figure 4. Sensitivity of the 60 human cancer cell lines to the cytotoxic activities of compound NSC 762256

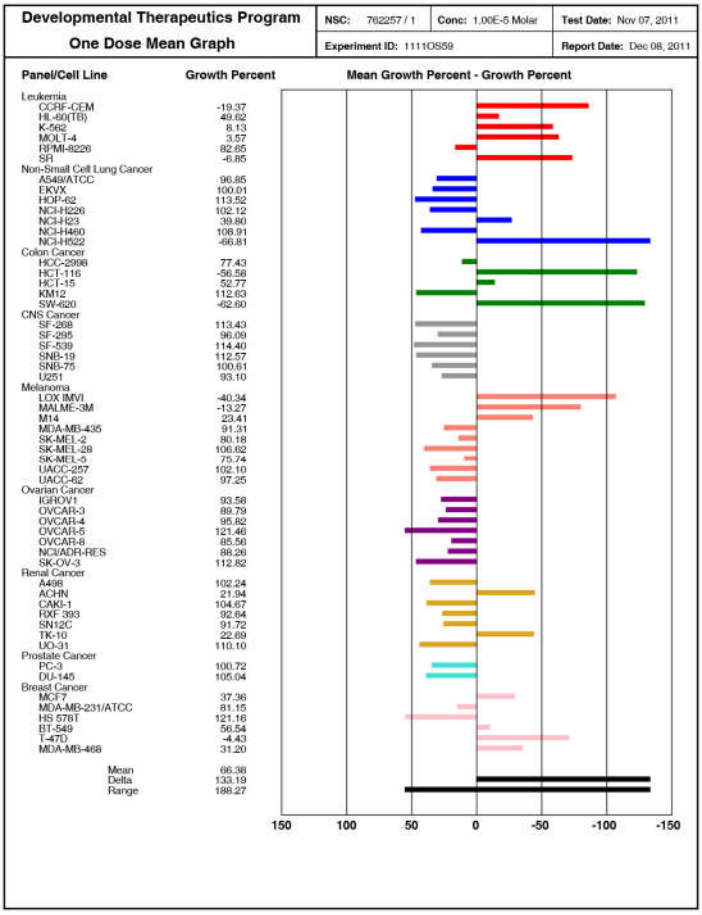


Figure 5. Sensitivity of the 60 human cancer cell lines to the cytotoxic activities of compound NSC 762257

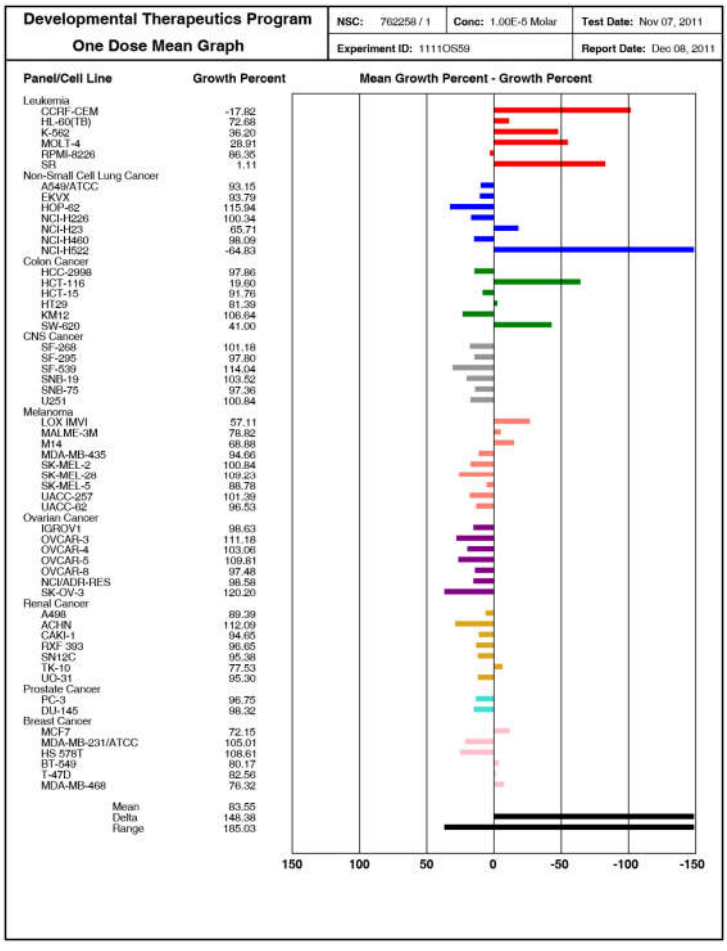


Figure 6. Sensitivity of the 60 human cancer cell lines to the cytotoxic activities of compound NSC 762258

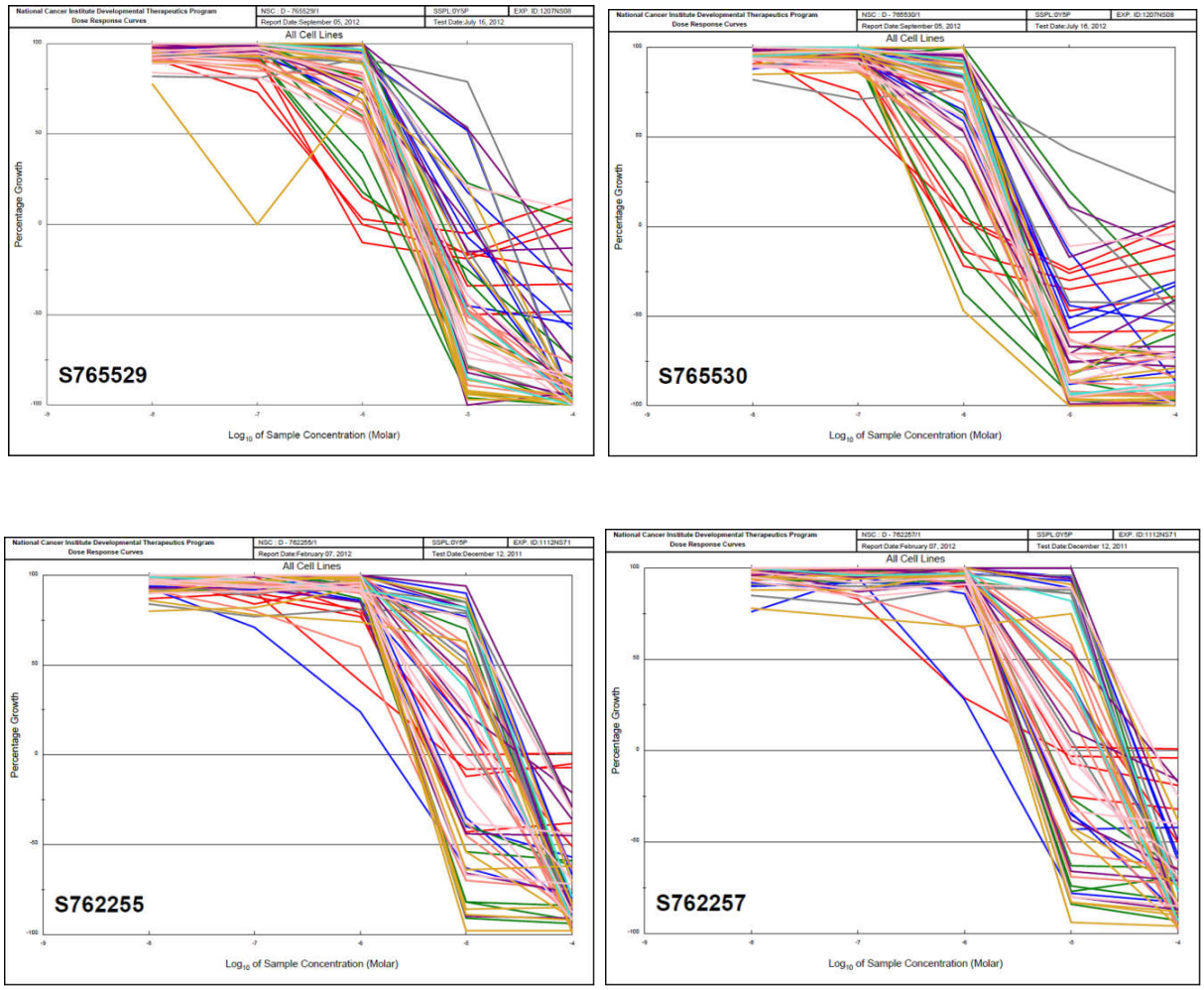


Figure 7. Collective Dose Response Curves of Compound NSC 765529, NSC 765530, NSC 762255 and NSC 762257 for all NCI 60 Cell Lines of *in Vitro* 5 Dose Assay

For NSC 765529, the NCI-60 GI_{50} values ranged from 0.21 µM to 16.9 µM. The leukemia cell lines showed a significant sensitivity to this compound; for out of five of the tested cell lines namely SR, CCRF-CEM, MOLT-4 and K-562 showed sub-micro molar GI_{50} values as small as 0.21, 0.24, 0.26 and 0.35 µM, respectively, followed colon cancer HCT-15, HCT-116, and SW-620 cell lines showing sub-micro molar GI_{50} values of 0.38, 0.43 and 0.68 µM, respectively. The least growth inhibitory activity was for the CNS cancer SNB-75 cell line (GI_{50} = 16.9 µM) (Table 1, Fig. 8). The compound NSC 765530 had a broad action spectrum.

The NCI-60 GI_{50} values ranged from 0.15 µM to 6.4 µM; the most sensitive cell lines were the leukemia SR, CCRF-CEM, MOLT-4 and K-562 (0.15, 0.19, 0.25, 0.30 µM respectively), colon cancer HCT-116, HCT-15, SW-620 and COLO 205 (0.21, 0.25, 0.35, 0.50 µM respectively), melanoma MALME-3M, LOX IMVI, MDA-MB-435 and M14 (0.30, 0.57, 0.62, 0.79 µM respectively), ovarian cancer OVCAR-8 and breast cancer MCF-7 cell lines showing sub-micro molar GI_{50} values of 0.60 and 0.78 µM respectively. The least growth inhibitory activity was for the non-Small cell lung cancer NCI-H322M cell line (GI_{50} = 6.4 µM) (Table 1, Fig. 8). The profiles of the compounds NSC 762255 and NSC 762257 are slightly different as well as their GI_{50} values for the most sensitive cell lines: the leukemia CCRF-CEM cell line (0.67 and 0.41 µM respectively), and the non-Small cell lung cancer NCI-H522 cell line (0.28 and 0.47 µM respectively).

For these compounds, the NCI-60 GI_{50} values ranged from 0.3 to 23 µM. (Table 1, Fig. 8). COMPARE correlation analysis (Boyd *et al*, 1995) showed similar response profiles for NSC 765529 and NSC 765530 ($r > 0.8$ for GI_{50}, TGI and LC_{50}), while NSC 762255 and NSC 762257 were almost identical ($r > 0.95$ for GI_{50}, TGI, and LC_{50}). Between NSC 765529 or 765530 and NSC 762255 or 762257, GI_{50} COMPARE averaged 0.65 (TGI = 0.56, LC_{50} = 0.61), indicating similarity in cell response. The high correlation of NSC 765529 and 765530, and of NSC 762255 and 762257 relative to between those groups may be explained by the concurrent testing of those pairs in the same NCI experiment.

Ultimately, all four compounds resulted in similar NCI-60 patterns. Among the four reported compounds, NSC 765530 provided the most potent and widest range of activity, and was therefore used as a seed to search the NCI standard agents database using the COMPARE algorithm. The highest variability in cell responses was obtained with the LC_{50} vector (SD = 0.55; GI_{50} and TGI SD values were 0.35 and 0.39, respectively), so that was the seed vector for comparison with LC_{50} (Table 2). Additionally, all public synthetic agents were examined for LC_{50} COMPARE correlations exceeding 0.7 with NSC 765530 LC_{50} values (Supplementary table). Among the 78 substances with $r > 0.7$, there were 23 with structures that contain quinones, including urdamycin A (NSC 613244, r=0.79) and cycloalkannin (NSC 301457, r = 0.71). The second-highest COMPARE correlation was for NSC 40342

Table 1. Cytotoxic activities of NSC 765529, NSC 765530, NSC 762255, and NSC 762257 against the NCI 60 human cancer cell lines

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 765529 / 1	Experiment ID : 1207NS08	Test Type : 08	Units : Molar
Report Date : September 05, 2012	Test Date : July 16, 2012	QNS :	MC :
COMI : KOR100008 (116962)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y5P	

		Log10 Concentration													
	Time	Mean Optical Densities						Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.627	2.704	2.560	2.281	0.626	0.527	0.465	93	80	.	-16	-26	2.35E-7	9.93E-7	> 1.00E-4
HL-60(TB)	0.895	2.554	2.498	2.410	2.219	0.445	0.469	97	91	80	-50	-48	1.70E-6	4.10E-6	.
K-562	0.240	1.922	1.877	1.774	0.497	0.200	0.309	97	91	15	-17	4	3.49E-7	.	> 1.00E-4
MOLT-4	0.664	2.325	2.312	2.219	0.599	0.539	0.654	99	94	-10	-19	-2	2.64E-7	8.03E-7	> 1.00E-4
RPMI-8226	1.272	2.857	2.778	2.761	2.572	0.840	0.849	95	95	82	-34	-33	1.89E-6	5.09E-6	> 1.00E-4
SR	0.221	0.610	0.578	0.504	0.234	0.209	0.276	92	73	3	-5	14	2.13E-7	.	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.400	1.817	1.828	1.831	1.742	0.660	0.251	101	101	95	18	-37	3.85E-6	2.14E-5	> 1.00E-4
HOP-62	0.410	1.337	1.363	1.317	1.335	0.455	-0.006	103	98	100	5	-100	3.34E-6	1.11E-5	3.34E-5
HOP-92	1.410	1.900	1.857	1.884	1.895	1.129	0.034	91	97	99	-20	-98	2.58E-6	6.79E-6	2.44E-5
NCI-H226	0.904	2.413	2.353	2.460	1.844	0.501	0.408	96	103	62	-45	-55	1.30E-6	3.62E-6	3.34E-5
NCI-H23	0.821	2.349	2.271	2.269	1.869	0.431	0.029	95	95	69	-48	-96	1.44E-6	3.89E-6	1.12E-5
NCI-H322M	0.815	1.746	1.719	1.739	1.668	1.301	0.023	97	99	92	52	-97	1.03E-5	2.24E-5	4.83E-5
NCI-H460	0.264	2.476	2.558	2.532	2.415	0.246	0.111	104	103	97	-7	-58	2.84E-6	8.57E-6	6.98E-5
Colon Cancer															
COLO 205	0.380	1.656	1.730	1.737	1.147	0.017	-0.013	106	106	60	-96	-100	1.16E-6	2.43E-6	5.09E-6
HCC-2998	1.199	3.281	3.189	3.247	3.298	0.826	0.103	96	98	101	-31	-91	2.43E-6	5.81E-6	2.06E-5
HCT-116	0.187	1.745	1.648	1.649	0.575	0.011	0.006	94	94	25	-94	-97	4.32E-7	1.62E-6	4.26E-6
HCT-15	0.160	1.814	1.700	1.710	0.455	0.120	0.041	93	94	18	-25	-74	3.77E-7	2.61E-6	3.21E-5
HT29	0.303	1.552	1.541	1.567	1.307	0.122	0.045	99	101	80	-60	-85	1.65E-6	3.75E-6	8.52E-6
KM12	0.409	2.145	2.148	2.164	2.229	0.809	0.432	100	101	105	23	1	4.68E-6	> 1.00E-4	> 1.00E-4
SW-620	0.247	2.036	2.076	2.037	0.959	0.051	0.001	102	100	40	-79	-100	6.77E-7	2.16E-6	5.67E-6
CNS Cancer															
SF-268	0.562	1.943	1.895	1.879	1.929	0.679	0.027	97	95	99	8	-95	3.48E-6	1.21E-5	3.66E-5
SF-539	0.493	2.184	2.190	2.323	2.217	0.109	0.013	100	106	102	-78	-97	1.95E-6	3.69E-6	7.00E-6
SNB-19	0.824	2.258	2.172	2.147	2.117	1.602	-0.002	94	92	90	54	-100	1.07E-5	2.25E-5	4.74E-5
SNB-75	1.227	2.227	2.052	2.035	2.147	2.019	0.632	82	81	92	79	-49	1.69E-5	4.17E-5	> 1.00E-4
U251	0.496	2.066	2.012	1.985	1.891	0.429	0.002	97	95	89	-14	-100	2.40E-6	7.38E-6	2.65E-5
Melanoma															
LOX IMVI	0.715	3.148	2.946	2.821	2.113	0.055	0.012	92	87	57	-92	-98	1.12E-6	2.42E-6	5.21E-6
MALME-3M	0.563	1.047	1.065	1.054	0.889	0.299	0.062	104	101	67	-47	-89	1.42E-6	3.88E-6	1.16E-5
M14	0.445	1.884	1.783	1.742	1.351	0.220	0.101	93	90	63	-51	-77	1.30E-6	3.59E-6	9.89E-6
MDA-MB-435	0.376	1.652	1.611	1.576	1.127	0.074	0.045	97	94	59	-80	-88	1.16E-6	2.65E-6	6.06E-6
SK-MEL-2	1.033	1.901	1.892	1.886	1.832	0.540	0.053	99	98	92	-48	-95	2.00E-6	4.55E-6	1.11E-5
SK-MEL-28	0.539	1.412	1.424	1.398	1.357	0.251	0.019	101	98	94	-54	-96	1.98E-6	4.33E-6	9.46E-6
SK-MEL-5	0.676	3.015	2.950	2.931	2.636	0.074	0.027	97	96	84	-89	-96	1.57E-6	3.05E-6	5.94E-6
UACC-257	0.900	1.765	1.688	1.638	1.606	0.133	0.023	91	85	82	-85	-98	1.55E-6	3.08E-6	6.15E-6
UACC-62	1.049	2.937	2.933	2.895	2.762	0.568	0.004	100	98	91	-44	-100	2.01E-6	4.72E-6	1.28E-5
Ovarian Cancer															
IGROV1	0.638	1.769	1.775	1.729	1.523	0.389	0.043	100	96	78	-39	-93	1.74E-6	4.64E-6	1.59E-5
OVCAR-3	0.485	1.585	1.666	1.662	1.538	0.086	0.025	107	107	96	-82	-95	1.81E-6	3.45E-6	6.58E-6
OVCAR-4	0.769	1.522	1.530	1.534	1.460	-0.002	0.050	101	102	94	-100	-93	1.69E-6	3.06E-6	5.53E-6
OVCAR-5	0.434	1.327	1.342	1.358	1.361	0.060	0.019	102	103	104	-86	-96	1.92E-6	3.52E-6	6.44E-6
OVCAR-8	0.417	1.746	1.750	1.805	1.383	0.426	0.100	100	104	73	1	-76	2.06E-6	1.02E-5	4.58E-5
NCI/ADR-RES	0.748	2.330	2.295	2.245	2.322	0.640	0.654	98	95	100	-15	-13	2.72E-6	7.46E-6	> 1.00E-4
SK-OV-3	0.592	1.350	1.334	1.344	1.380	0.991	0.454	98	99	104	53	-23	1.08E-5	4.93E-5	> 1.00E-4
Renal Cancer															
786-0	0.838	2.854	2.850	2.870	2.768	0.336	0.081	100	101	96	-60	-90	1.97E-6	4.12E-6	8.64E-6
A498	1.396	2.096	1.944	.	1.921	1.541	0.026	78	.	75	21	-98	2.89E-6	1.49E-5	3.93E-5
ACHN	0.259	1.534	1.597	1.587	1.214	0.008	0.008	105	104	75	-97	-97	1.40E-6	2.73E-6	5.33E-6
CAKI-1	1.099	2.981	2.891	2.853	2.831	0.155	0.042	95	93	92	-86	-96	1.72E-6	3.29E-6	6.28E-6
RXF 393	0.885	1.249	1.276	1.261	1.250	0.074	0.014	107	103	100	-92	-98	1.83E-6	3.33E-6	6.06E-6
SN12C	0.958	2.950	2.872	2.919	2.740	0.773	0.064	96	98	89	-19	-93	2.30E-6	6.64E-6	2.59E-5
TK-10	0.779	1.328	1.334	1.341	1.394	0.045	-0.006	101	102	112	-94	-100	2.00E-6	3.49E-6	6.10E-6
UO-31	0.680	2.044	1.910	1.881	1.622	0.046	0.011	90	88	69	-93	-98	1.31E-6	2.66E-6	5.41E-6
Prostate Cancer															
PC-3	0.518	1.952	1.966	1.951	1.834	0.262	0.014	101	100	92	-49	-97	1.98E-6	4.47E-6	1.03E-5
DU-145	0.389	1.532	1.573	1.528	1.502	0.059	.	104	100	97	-85	-100	1.82E-6	3.42E-6	6.43E-6
Breast Cancer															
MCF7	0.424	2.358	2.058	2.001	1.507	0.168	-0.009	84	82	56	-60	-100	1.13E-6	3.03E-6	8.14E-6
MDA-MB-231/ATCC	0.677	1.467	1.505	1.501	1.422	0.415	0.079	105	104	94	-39	-88	2.15E-6	5.12E-6	1.69E-5
HS 578T	0.912	2.066	2.037	2.064	1.992	1.154	1.006	96	98	92	21	8	3.67E-6	> 1.00E-4	> 1.00E-4
BT-549	0.746	2.010	1.936	1.972	1.748	0.228	0.071	94	97	79	-70	-91	1.57E-6	3.41E-6	7.39E-6
T-47D	0.684	1.641	1.562	1.594	1.477	0.230	0.088	92	95	83	-66	-87	1.66E-6	3.59E-6	7.77E-6
MDA-MB-468	0.767	1.664	1.564	1.563	1.323	0.198	0.129	89	89	62	-74	-83	1.22E-6	2.85E-6	6.64E-6

Continue……..

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 765530 / 1	Experiment ID : 1207NS08	Test Type : 08	Units : Molar
Report Date : September 05, 2012	Test Date : July 16, 2012	QNS :	MC :
COMI : KOR100009 (116963)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y5P	

			Log10 Concentration												
	Time		Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.627	2.705	2.553	2.186	0.537	0.441	0.525	93	75	-14	-30	-16	1.91E-7	6.91E-7	> 1.00E-4
HL-60(TB)	0.895	2.611	2.464	2.424	2.190	0.371	0.378	91	89	75	-59	-58	1.55E-6	3.65E-6	8.63E-6
K-562	0.240	1.820	1.773	1.691	0.283	0.177	0.222	97	92	3	-26	-8	2.95E-7	1.24E-6	> 1.00E-4
MOLT-4	0.664	2.168	2.152	2.104	0.520	0.433	0.504	99	96	-22	-35	-24	2.45E-7	6.53E-7	> 1.00E-4
RPMI-8226	1.272	2.837	2.766	2.764	2.483	0.677	0.772	95	95	77	-47	-39	1.66E-6	4.20E-6	> 1.00E-4
SR	0.221	0.582	0.578	0.439	0.241	0.169	0.226	99	60	5	-24	1	1.54E-7	.	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.400	1.809	1.780	1.742	1.695	0.173	0.270	98	95	92	-57	-33	1.91E-6	4.15E-6	.
HOP-62	0.410	1.328	1.315	1.336	1.284	0.013	0.011	99	101	95	-97	-97	1.72E-6	3.13E-6	5.70E-6
HOP-92	1.410	1.867	1.854	1.862	1.843	0.169	0.273	97	99	95	-88	-81	1.76E-6	3.30E-6	6.20E-6
NCI-H226	0.904	2.389	2.339	2.307	1.866	0.507	0.412	97	94	65	-44	-54	1.37E-6	3.95E-6	3.77E-5
NCI-H23	0.821	2.311	2.277	2.228	1.696	0.153	0.222	98	94	59	-81	-73	1.15E-6	2.62E-6	5.97E-6
NCI-H322M	0.815	1.721	1.609	1.686	1.655	0.701	0.116	88	96	93	-14	-86	2.51E-6	7.39E-6	3.17E-5
NCI-H460	0.264	2.405	2.471	2.555	2.242	0.129	0.182	103	107	92	-51	-31	1.97E-6	4.40E-6	.
Colon Cancer															
COLO 205	0.380	1.655	1.757	1.847	0.653	0.012	-0.015	108	115	21	-97	-100	4.95E-7	1.52E-6	4.01E-6
HCC-2998	1.199	3.247	3.215	3.221	3.318	0.173	0.037	98	99	103	-86	-97	1.92E-6	3.53E-6	6.48E-6
HCT-116	0.187	1.852	1.826	1.730	0.118	0.013	0.014	98	93	-37	-93	-93	2.13E-7	5.19E-7	1.71E-6
HCT-15	0.160	1.751	1.651	1.625	0.134	0.026	0.064	94	92	-16	-83	-60	2.45E-7	7.08E-7	3.23E-6
HT29	0.303	1.502	1.539	1.580	1.064	0.102	0.089	103	106	63	-67	-71	1.27E-6	3.08E-6	7.46E-6
KM12	0.409	2.135	2.090	2.043	2.141	0.748	0.238	97	95	100	20	-42	4.21E-6	2.09E-5	> 1.00E-4
SW-620	0.247	2.007	2.055	2.003	0.382	0.062	0.056	103	100	8	-75	-78	3.47E-7	1.24E-6	4.97E-6
CNS Cancer															
SF-268	0.562	1.985	1.917	1.905	1.738	0.329	0.322	95	94	83	-42	-43	1.83E-6	4.63E-6	> 1.00E-4
SF-539	0.493	2.145	2.197	2.227	2.037	0.002	0.009	103	105	93	-100	-98	1.68E-6	3.05E-6	5.53E-6
SNB-19	0.824	2.268	2.124	2.170	2.092	0.975	0.426	90	93	88	10	-48	3.08E-6	1.51E-5	> 1.00E-4
SNB-75	1.227	2.257	2.072	1.960	2.019	1.673	1.422	82	71	77	43	19	6.32E-6	> 1.00E-4	> 1.00E-4
U251	0.496	2.049	2.014	1.950	1.873	0.013	0.008	98	94	89	-97	-98	1.61E-6	3.00E-6	5.56E-6
Melanoma															
LOX IMVI	0.715	3.147	2.989	2.825	1.637	0.057	0.041	94	87	38	-92	-94	5.66E-7	1.96E-6	4.74E-6
MALME-3M	0.563	1.063	1.036	1.077	0.516	0.164	0.169	95	103	-8	-71	-70	2.99E-7	8.41E-7	4.64E-6
M14	0.445	1.759	1.675	1.668	1.036	0.057	0.051	94	93	45	-87	-89	7.87E-7	2.19E-6	5.22E-6
MDA-MB-435	0.376	1.661	1.538	1.503	0.890	0.018	0.031	90	88	40	-95	-92	6.16E-7	1.97E-6	4.62E-6
SK-MEL-2	1.033	1.860	1.849	1.812	1.682	0.197	0.291	99	94	78	-81	-72	1.51E-6	3.11E-6	6.40E-6
SK-MEL-28	0.539	1.450	1.437	1.401	1.371	0.198	0.088	99	95	91	-63	-84	1.85E-6	3.90E-6	8.21E-6
SK-MEL-5	0.676	3.041	2.963	2.920	2.318	0.001	0.036	97	95	69	-100	-95	1.30E-6	2.57E-6	5.07E-6
UACC-257	0.900	1.657	1.636	1.578	1.499	0.042	0.061	97	90	79	-95	-93	1.47E-6	2.84E-6	5.49E-6
UACC-62	1.049	2.906	2.815	2.817	2.636	0.002	0.017	95	95	85	-100	-98	1.55E-6	2.89E-6	5.38E-6
Ovarian Cancer															
IGROV1	0.538	1.831	1.803	1.758	1.271	0.150	0.192	98	94	53	-76	-70	1.06E-6	2.57E-6	6.24E-6
OVCAR-3	0.485	1.579	1.668	1.672	1.072	0.122	0.106	108	108	54	-75	-78	1.07E-6	2.61E-6	6.40E-6
OVCAR-4	0.769	1.570	1.564	1.521	1.444	0.251	0.254	99	94	84	-67	-67	1.68E-6	3.59E-6	7.68E-6
OVCAR-5	0.434	1.334	1.316	1.356	1.294	0.003	0.010	98	102	96	-99	-98	1.71E-6	3.09E-6	5.58E-6
OVCAR-8	0.417	1.640	1.690	1.611	0.860	0.121	0.246	104	98	36	-71	-41	5.96E-7	2.18E-6	.
NCI/ADR-RES	0.748	2.328	2.310	2.294	2.246	0.618	0.789	99	98	95	-17	3	2.51E-6	.	> 1.00E-4
SK-OV-3	0.592	1.330	1.310	1.370	1.302	0.672	0.517	97	105	96	11	-13	3.48E-6	2.89E-5	> 1.00E-4
Renal Cancer															
786-0	0.838	2.861	2.865	2.855	2.618	0.121	0.174	100	100	88	-86	-79	1.66E-6	3.21E-6	6.23E-6
A498	1.396	2.007	1.986	2.049	1.950	0.503	0.358	97	107	91	-64	-74	1.83E-6	3.86E-6	8.12E-6
ACHN	0.259	1.545	1.635	1.606	0.138	0.001	0.001	107	104	-47	-100	-100	2.29E-7	4.90E-7	1.14E-6
CAKI-1	1.099	2.940	2.832	2.854	2.513	0.155	0.176	94	95	77	-86	-84	1.46E-6	2.96E-6	6.01E-6
RXF 393	0.885	1.255	1.218	1.287	1.177	0.058	0.046	90	109	79	-94	-95	1.47E-6	2.87E-6	5.59E-6
SN12C	0.958	2.849	2.786	2.799	2.445	0.159	0.443	97	97	79	-83	-54	1.50E-6	3.06E-6	6.22E-6
TK-10	0.779	1.345	1.321	1.353	1.413	0.033	0.019	96	101	112	-96	-98	1.98E-6	3.46E-6	6.02E-6
UO-31	0.680	2.038	1.837	1.844	1.292	0.019	0.027	85	86	45	-97	-96	7.57E-7	2.07E-6	4.65E-6
Prostate Cancer															
PC-3	0.518	2.003	1.922	1.977	1.777	0.035	0.045	95	98	85	-93	-91	1.57E-6	2.99E-6	5.72E-6
DU-145	0.389	1.583	1.625	1.586	1.484	0.022	0.049	103	100	92	-94	-87	1.68E-6	3.11E-6	5.77E-6
Breast Cancer															
MCF7	0.424	2.294	2.162	2.113	1.265	0.124	0.005	93	90	45	-71	-99	7.75E-7	2.45E-6	6.62E-6
MDA-MB-231/ATCC	0.677	1.395	1.438	1.389	1.251	0.085	0.193	106	99	80	-87	-72	1.51E-6	3.00E-6	5.97E-6
HS 578T	0.912	1.993	1.962	1.973	1.965	0.813	0.877	97	98	97	-11	-4	2.74E-6	7.93E-6	> 1.00E-4
BT-549	0.746	2.074	1.991	1.970	1.757	0.037	0.092	94	92	76	-95	-88	1.42E-6	2.78E-6	5.45E-6
T-47D	0.684	1.693	1.586	1.574	1.304	0.243	0.202	89	88	61	-64	-71	1.23E-6	3.07E-6	7.67E-6
MDA-MB-468	0.767	1.671	1.581	1.573	1.261	0.221	0.197	90	89	55	-71	-74	1.09E-6	2.72E-6	6.78E-6

Continue……..

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 762255 / 1	Experiment ID : 1112NS71	Test Type : 08	Units : Molar
Report Date : February 07, 2012	Test Date : December 12, 2011	QNS :	MC :
COMI : PSG1400005 (110477)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y5P	

Log10 Concentration

Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.438	1.886	1.887	1.760	1.034	0.402	0.409	100	91	41	-8	-7	6.66E-7	6.79E-6	> 1.00E-4
HL-60(TB)	0.860	2.556	2.557	2.279	2.483	1.150	0.418	100	84	96	17	-51	3.81E-6	1.76E-5	9.54E-5
K-562	0.167	1.210	1.184	1.083	0.973	0.167	0.174	98	88	77	.	1	2.25E-6	> 1.00E-4	> 1.00E-4
MOLT-4	0.461	1.689	1.710	1.672	1.437	0.261	0.286	102	99	79	-43	-38	1.74E-6	4.43E-6	> 1.00E-4
SR	0.316	1.612	1.445	1.484	1.364	0.278	0.301	87	90	81	-12	-5	2.14E-6	7.40E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.314	1.509	1.462	1.453	1.412	1.239	0.115	96	95	92	77	-64	1.56E-5	3.54E-5	8.02E-5
EKVX	0.576	1.236	1.199	1.186	1.146	0.348	0.250	94	92	86	-40	-57	1.94E-6	4.85E-6	4.09E-5
HOP-62	0.303	0.705	0.696	0.680	0.734	0.534	0.060	98	94	107	57	-80	1.13E-5	2.61E-5	6.03E-5
HOP-92	0.968	1.396	1.392	1.384	1.403	0.642	0.140	99	97	102	-35	-86	2.39E-6	5.54E-6	1.97E-5
NCI-H226	0.638	1.212	1.169	1.160	1.192	1.110	0.073	92	91	97	82	-89	1.54E-5	3.03E-5	5.94E-5
NCI-H23	0.861	2.316	2.241	2.259	2.112	1.121	0.145	95	96	86	18	-83	3.37E-6	1.50E-5	4.69E-5
NCI-H460	0.285	2.316	2.341	2.330	2.352	2.110	0.094	101	101	102	90	-67	1.80E-5	3.74E-5	7.79E-5
NCI-H522	0.678	1.438	1.385	1.217	0.859	0.251	0.141	93	71	24	-63	-79	2.78E-7	1.88E-6	7.09E-6
Colon Cancer															
COLO 205	0.279	0.909	0.912	0.942	1.026	0.027	0.017	100	105	119	-91	-94	2.13E-6	3.69E-6	6.40E-6
HCC-2998	0.591	1.951	1.933	2.031	1.837	1.547	0.042	99	106	92	70	-93	1.33E-5	2.69E-5	5.45E-5
HCT-116	0.219	1.509	1.467	1.611	1.442	0.040	0.035	97	108	95	-82	-84	1.79E-6	3.44E-6	6.59E-6
HCT-15	0.292	1.996	1.830	1.896	1.883	0.179	0.110	90	94	93	-39	-62	2.13E-6	5.08E-6	2.98E-5
HT29	0.198	1.112	1.128	1.109	1.165	0.092	0.081	102	100	106	-54	-59	2.24E-6	4.60E-6	9.47E-6
KM12	0.493	1.960	1.952	1.986	2.006	1.738	0.077	99	102	103	85	-84	1.61E-5	3.17E-5	6.26E-5
SW-620	0.244	1.555	1.525	1.568	1.382	0.044	0.019	98	101	87	-82	-92	1.65E-6	3.26E-6	6.45E-6
CNS Cancer															
SF-268	0.496	1.496	1.427	1.385	1.488	1.024	0.083	93	89	99	53	-83	1.05E-5	2.44E-5	5.69E-5
SF-295	0.819	2.433	2.288	2.287	2.304	2.188	0.576	91	91	92	85	-30	2.01E-5	5.51E-5	> 1.00E-4
SF-539	0.695	1.772	1.771	1.756	1.859	0.767	0.092	100	99	108	7	-87	3.74E-6	1.18E-5	4.04E-5
SNB-19	0.650	1.961	1.852	1.863	1.871	1.694	0.012	92	93	93	80	-98	1.47E-5	2.80E-5	5.36E-5
SNB-75	0.735	1.280	1.193	1.156	1.176	1.163	0.058	84	77	81	79	-92	1.47E-5	2.89E-5	5.66E-5
Melanoma															
LOX IMVI	0.255	1.555	1.455	1.301	1.039	0.077	0.065	92	80	60	-70	-75	1.20E-6	2.91E-6	7.04E-6
MALME-3M	0.588	1.676	1.670	1.687	1.656	1.218	0.091	99	101	98	58	-85	1.14E-5	2.55E-5	5.72E-5
M14	0.415	1.200	1.165	1.231	1.176	0.227	0.051	96	104	97	-45	-88	2.14E-6	4.80E-6	1.29E-5
MDA-MB-435	0.473	1.863	1.806	1.726	1.815	0.633	0.045	96	90	97	11	-91	3.52E-6	1.30E-5	4.00E-5
SK-MEL-2	0.861	1.674	1.680	1.694	1.756	1.365	0.308	101	102	110	62	-64	1.24E-5	3.10E-5	7.71E-5
SK-MEL-28	0.507	1.253	1.270	1.272	1.269	0.825	0.025	102	103	102	43	-95	7.52E-6	2.04E-5	4.71E-5
SK-MEL-5	0.523	2.438	2.353	2.340	2.338	1.314	0.013	96	95	95	41	-98	6.88E-6	1.98E-5	4.55E-5
UACC-257	0.550	1.205	1.193	1.170	1.151	0.344	0.054	98	95	92	-38	-90	2.10E-6	5.12E-6	1.72E-5
UACC-62	0.579	2.099	2.064	2.050	1.946	0.921	0.011	98	97	90	22	-98	3.91E-6	1.54E-5	3.99E-5
Ovarian Cancer															
IGROV1	0.590	1.302	1.250	1.256	1.194	0.200	0.135	93	93	85	-66	-77	1.70E-6	3.64E-6	7.81E-6
OVCAR-3	0.517	1.284	1.281	1.295	1.330	0.053	0.045	100	101	106	-90	-91	1.93E-6	3.48E-6	6.26E-6
OVCAR-4	0.534	1.079	1.079	1.082	1.043	0.298	0.296	100	101	93	-44	-45	2.07E-6	4.77E-6	> 1.00E-4
OVCAR-5	0.597	1.619	1.613	1.577	1.662	1.440	0.076	99	96	104	82	-87	1.55E-5	3.06E-5	6.03E-5
OVCAR-8	0.417	1.712	1.674	1.735	1.776	0.717	0.331	97	102	105	23	-21	4.70E-6	3.38E-5	> 1.00E-4
NCI/ADR-RES	0.532	1.693	1.749	1.755	1.734	1.029	0.339	105	105	103	43	-36	7.60E-6	3.47E-5	> 1.00E-4
SK-OV-3	0.487	1.032	1.034	1.027	1.070	1.000	0.347	100	99	107	94	-29	2.29E-5	5.83E-5	> 1.00E-4
Renal Cancer															
786-0	0.834	2.265	2.187	2.223	2.244	2.084	0.244	95	97	99	87	-71	1.72E-5	3.57E-5	7.39E-5
A498	1.307	1.793	1.723	1.687	1.668	1.612	0.016	86	78	74	63	-99	1.20E-5	2.45E-5	4.99E-5
ACHN	0.312	1.406	1.461	1.376	1.450	0.043	0.046	105	97	104	-86	-85	1.92E-6	3.52E-6	6.45E-6
CAKI-1	0.638	2.085	1.957	1.948	2.035	0.233	0.240	91	91	97	-64	-62	1.95E-6	4.01E-6	8.23E-6
RXF 393	0.656	1.039	1.024	1.025	1.081	0.015	0.014	96	96	111	-98	-98	1.96E-6	3.40E-6	5.90E-6
SN12C	0.466	1.867	1.841	1.891	1.824	1.167	0.079	98	102	97	50	-83	1.00E-5	2.38E-5	5.64E-5
TK-10	0.738	1.319	1.259	1.301	1.363	0.341	0.068	90	97	108	-54	-91	2.27E-6	4.64E-6	9.46E-6
UO-31	0.555	1.661	1.443	1.459	1.588	0.061	0.044	80	82	93	-89	-92	1.73E-6	3.25E-6	6.11E-6
Prostate Cancer															
PC-3	0.513	1.809	1.801	1.768	1.710	1.576	0.106	99	97	92	82	-79	1.58E-5	3.22E-5	6.56E-5
DU-145	0.381	1.160	1.208	1.170	1.173	0.667	0.031	106	101	102	37	-92	6.24E-6	1.93E-5	4.72E-5
Breast Cancer															
MCF7	0.268	1.497	1.475	1.420	1.385	0.267	0.081	98	94	91	-1	-70	2.80E-6	9.86E-6	5.16E-5
MDA-MB-231/ATCC	0.490	1.160	1.166	1.181	1.107	0.676	0.059	101	103	92	28	-88	4.50E-6	1.74E-5	4.70E-5
HS 578T	1.204	1.983	1.959	1.960	1.915	1.793	0.830	97	97	91	76	-31	1.74E-5	5.11E-5	> 1.00E-4
BT-549	0.840	1.436	1.407	1.480	1.466	0.661	0.068	95	107	105	-21	-92	2.72E-6	6.76E-6	2.55E-5
T-47D	0.624	1.468	1.388	1.393	1.417	0.387	0.353	90	91	94	-38	-44	2.15E-6	5.15E-6	> 1.00E-4
MDA-MB-468	0.549	0.782	0.774	0.766	0.772	0.183	0.152	96	93	96	-67	-72	1.91E-6	3.88E-6	7.89E-6

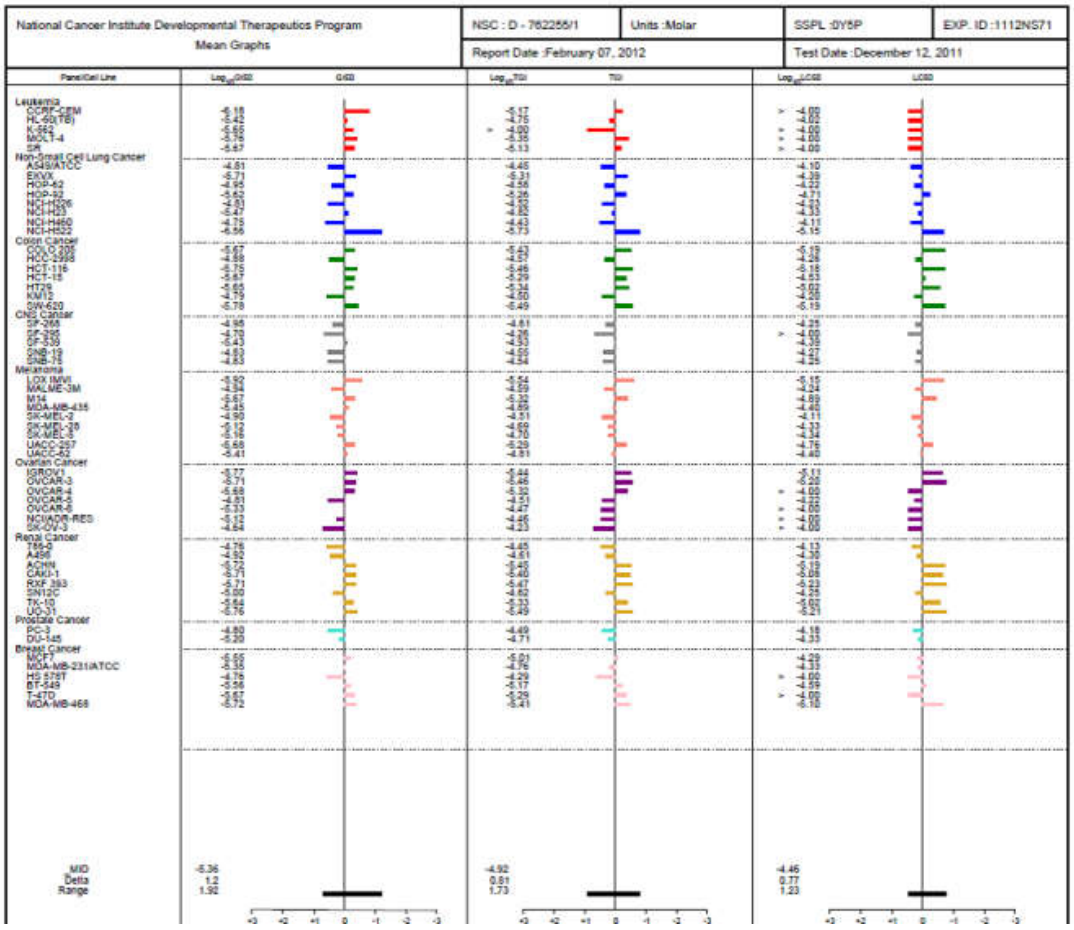
Continue……..

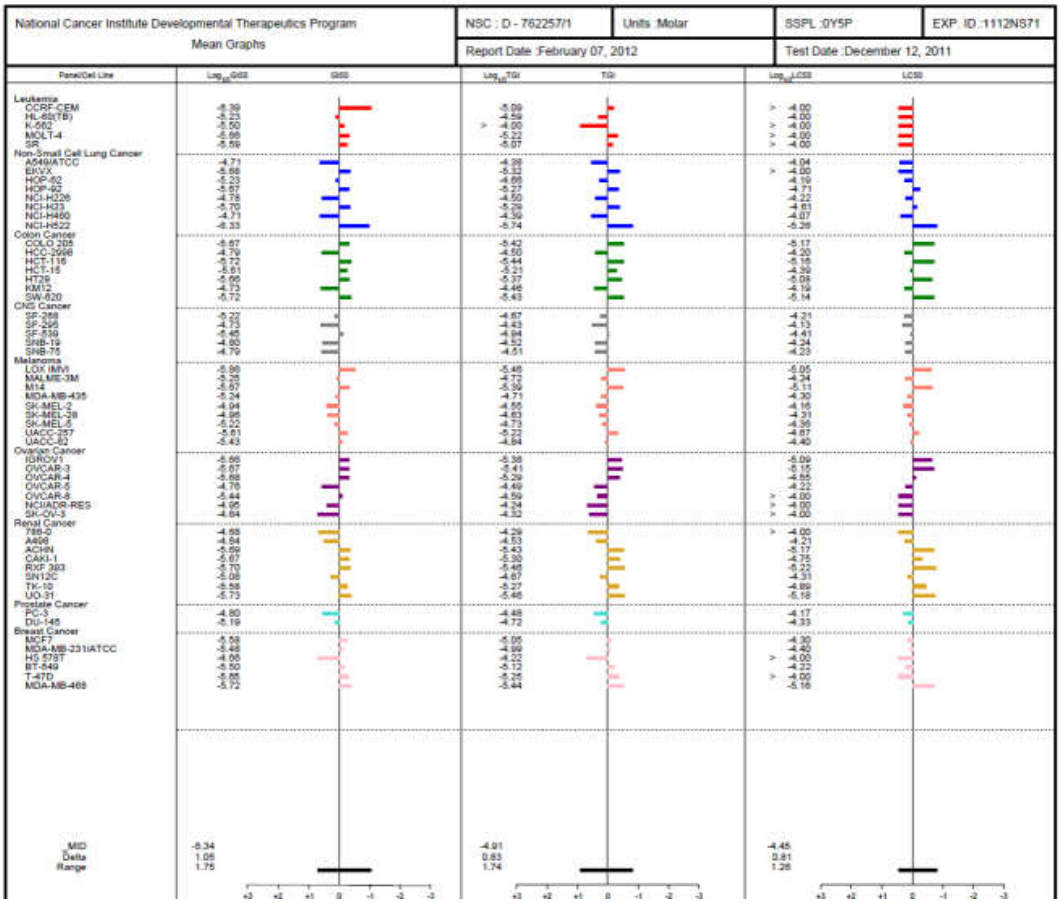
National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 762257 / 1	Experiment ID : 1112NS71	Test Type : 08	Units : Molar
Report Date : February 07, 2012	Test Date : December 12, 2011	QNS :	MC :
COMI : PSG1400007 (110479)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0Y5P	

Log10 Concentration

Panel/Cell Line	Time Zero	Mean Optical Densities Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	Percent Growth -8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.438	1.905	1.907	1.661	0.859	0.426	0.421	100	83	29	-3	-4	4.07E-7	8.18E-6	> 1.00E-4
HL-60(TB)	0.860	2.847	2.861	2.938	2.909	1.541	0.429	101	105	103	34	-50	5.91E-6	2.54E-5	9.95E-5
K-562	0.167	1.346	1.379	1.340	1.319	0.192	0.176	103	99	98	2	1	3.15E-6	> 1.00E-4	> 1.00E-4
MOLT-4	0.461	1.761	1.869	2.094	1.614	0.345	0.314	108	126	89	-25	-32	2.19E-6	6.01E-6	> 1.00E-4
SR	0.316	1.696	1.600	1.706	1.552	0.295	0.258	93	101	90	-7	-19	2.58E-6	8.53E-6	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.314	1.500	1.496	1.437	1.461	1.415	0.136	100	95	97	93	-57	1.93E-5	4.18E-5	9.02E-5
EKVX	0.576	1.221	1.169	1.146	1.175	0.330	0.334	92	88	93	-43	-42	2.07E-6	4.84E-6	> 1.00E-4
HOP-62	0.303	0.711	0.711	0.717	0.692	0.453	0.091	100	102	95	37	-70	5.92E-6	2.20E-5	6.48E-5
HOP-92	0.988	1.371	1.333	1.339	1.338	0.655	0.110	90	92	91	-34	-89	2.14E-6	5.37E-6	1.97E-5
NCI-H226	0.638	1.237	1.273	1.245	1.267	1.172	0.073	106	101	105	89	-89	1.66E-5	3.17E-5	6.06E-5
NCI-H23	0.861	2.305	2.278	2.234	2.104	0.562	0.227	98	95	86	-35	-74	1.99E-6	5.16E-6	2.47E-5
NCI-H460	0.285	2.348	2.390	2.338	2.351	2.244	0.114	102	100	100	95	-60	1.95E-5	4.09E-5	8.60E-5
NCI-H522	0.678	1.444	1.258	1.405	0.890	0.150	0.113	76	95	28	-78	-83	4.65E-7	1.83E-6	5.44E-6
Colon Cancer															
COLO 205	0.279	0.916	0.970	0.992	1.011	0.045	0.020	108	112	115	-84	-93	2.12E-6	3.78E-6	6.74E-6
HCC-2998	0.591	1.933	1.847	1.823	1.832	1.747	0.090	94	92	93	86	-85	1.63E-5	3.19E-5	6.25E-5
HCT-116	0.219	1.630	1.681	1.693	1.616	0.050	0.066	104	104	99	-77	-69	1.90E-6	3.64E-6	6.99E-6
HCT-15	0.292	1.960	1.902	2.012	1.940	0.217	0.102	96	103	99	-26	-65	2.46E-6	6.22E-6	4.12E-5
HT29	0.198	1.123	1.161	1.185	1.203	0.073	0.072	104	107	109	-63	-64	2.20E-6	4.29E-6	8.39E-6
KM12	0.493	2.010	2.026	2.147	2.165	2.005	0.070	101	109	110	100	-86	1.85E-5	3.45E-5	6.41E-5
SW-620	0.244	1.571	1.551	1.541	1.552	0.063	0.043	98	98	99	-74	-82	1.91E-6	3.71E-6	7.23E-6
CNS Cancer															
SF-268	0.496	1.570	1.548	1.569	1.575	0.884	0.137	98	100	101	36	-72	6.08E-6	2.15E-5	6.21E-5
SF-295	0.819	2.459	2.388	2.331	2.394	2.387	0.238	96	92	96	96	-71	1.88E-5	3.75E-5	7.48E-5
SF-539	0.695	1.788	1.821	1.884	1.829	0.761	0.077	103	109	104	6	-89	3.55E-6	1.16E-5	3.89E-5
SNB-19	0.650	2.011	1.888	1.872	1.882	1.820	0.049	91	90	91	86	-93	1.59E-5	3.03E-5	5.78E-5
SNB-75	0.735	1.264	1.187	1.156	1.205	1.199	0.072	85	80	89	88	-90	1.63E-5	3.11E-5	5.94E-5
Melanoma															
LOX IMVI	0.255	1.562	1.504	1.366	1.130	0.112	0.093	96	85	67	-56	-64	1.37E-6	3.49E-6	8.89E-6
MALME-3M	0.568	1.768	1.805	1.851	1.886	0.937	0.145	103	107	110	30	-75	5.57E-6	1.91E-5	5.73E-5
M14	0.415	1.285	1.305	1.423	1.364	0.130	0.114	102	116	109	-69	-73	2.15E-6	4.11E-6	7.85E-6
MDA-MB-435	0.473	1.830	1.799	1.770	1.789	0.950	0.066	98	96	97	35	-86	5.76E-6	1.95E-5	5.04E-5
SK-MEL-2	0.861	1.647	1.743	1.769	1.779	1.320	0.253	112	116	117	58	-71	1.16E-5	2.83E-5	6.92E-5
SK-MEL-28	0.507	1.272	1.276	1.226	1.251	0.936	0.017	100	94	97	56	-97	1.09E-5	2.33E-5	4.94E-5
SK-MEL-5	0.523	2.489	2.599	2.557	2.527	1.223	0.012	106	103	102	36	-98	6.07E-6	1.85E-5	4.39E-5
UACC-257	0.550	1.210	1.189	1.188	1.205	0.394	0.038	97	97	99	-28	-93	2.43E-6	5.99E-6	2.15E-5
UACC-62	0.579	2.138	2.110	2.105	1.996	0.874	0.024	98	98	91	19	-96	3.70E-6	1.46E-5	3.98E-5
Ovarian Cancer															
IGROV1	0.590	1.345	1.331	1.341	1.414	0.202	0.172	98	99	109	-66	-71	2.18E-6	4.20E-6	8.12E-6
OVCAR-3	0.517	1.357	1.403	1.387	1.474	0.104	0.067	105	104	114	-80	-87	2.14E-6	3.87E-6	7.01E-6
OVCAR-4	0.534	1.106	1.105	1.031	1.060	0.332	0.188	100	87	92	-38	-65	2.11E-6	5.11E-6	2.81E-5
OVCAR-5	0.597	1.634	1.594	1.669	1.634	1.572	0.053	96	103	100	94	-91	1.73E-5	3.22E-5	5.99E-5
OVCAR-8	0.417	1.751	1.760	1.686	1.760	0.563	0.351	102	95	101	11	-16	3.67E-6	2.56E-5	> 1.00E-4
NCI/ADR-RES	0.532	1.736	1.751	1.750	1.687	1.177	0.444	101	101	96	54	-17	1.12E-5	5.79E-5	> 1.00E-4
SK-OV-3	0.487	1.006	1.037	1.066	1.046	1.043	0.246	106	111	108	107	-49	2.31E-5	4.83E-5	> 1.00E-4
Renal Cancer															
786-0	0.834	2.330	2.313	2.498	2.410	2.199	0.521	99	111	105	91	-38	2.09E-5	5.11E-5	> 1.00E-4
A498	1.307	1.838	1.719	1.695	1.667	1.703	0.214	78	73	68	75	-84	1.43E-5	2.96E-5	6.13E-5
ACHN	0.312	1.414	1.417	1.522	1.506	0.054	0.039	100	110	108	-83	-88	2.02E-6	3.69E-6	6.74E-6
CAKI-1	0.638	2.034	1.956	1.949	1.973	0.371	0.163	94	94	96	-42	-74	2.15E-6	4.96E-6	1.77E-5
RXF 393	0.656	1.097	1.100	1.171	1.144	0.039	0.026	101	117	111	-94	-96	1.98E-6	3.47E-6	6.09E-6
SN12C	0.466	1.941	1.869	1.880	1.864	1.145	0.031	95	96	95	46	-93	8.30E-6	2.14E-5	4.89E-5
TK-10	0.738	1.316	1.332	1.336	1.413	0.412	0.026	103	103	117	-44	-96	2.60E-6	5.32E-6	1.29E-5
UO-31	0.555	1.695	1.556	1.560	1.677	0.094	0.057	88	88	98	-83	-90	1.85E-6	3.48E-6	6.57E-6
Prostate Cancer															
PC-3	0.513	1.816	1.810	1.763	1.777	1.585	0.117	100	96	97	82	-77	1.59E-5	3.28E-5	6.75E-5
DU-145	0.381	1.266	1.353	1.341	1.307	0.709	0.025	110	108	105	37	-93	6.43E-6	1.92E-5	4.65E-5
Breast Cancer															
MCF7	0.268	1.573	1.480	1.367	1.430	0.256	0.082	93	84	89	-4	-69	2.61E-6	8.96E-6	5.03E-5
MDA-MB-231/ATCC	0.490	1.116	1.170	1.191	1.141	0.497	0.079	109	112	104	1	-84	3.34E-6	1.03E-5	3.99E-5
HS 578T	1.204	2.014	1.970	1.918	1.936	1.924	0.908	95	88	91	89	-25	2.20E-5	6.07E-5	> 1.00E-4
BT-549	0.840	1.471	1.498	1.581	1.574	0.712	0.339	104	117	116	-15	-60	3.19E-6	7.66E-6	6.07E-5
T-47D	0.624	1.441	1.422	1.373	1.403	0.421	0.378	98	92	95	-33	-40	2.26E-6	5.56E-6	> 1.00E-4
MDA-MB-468	0.549	0.794	0.817	0.800	0.798	0.111	0.081	110	103	102	-80	-85	1.93E-6	3.63E-6	6.85E-6


National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC : D - 762255/1
Units :Molar
SSPL :0Y5P
EXP. ID :1112NS71
Report Date :February 07, 2012
Test Date :December 12, 2011
Panel/Cell Line
Leukemia
CCRF-CEM
HL-60(TB)
K-562
MOLT-4
SR
Non-Small Cell Lung Cancer
A549/ATCC
EKVX
HOP-62
HOP-92
NCI-H226
NCI-H23
NCI-H460
NCI-H522
Colon Cancer
COLO 205
HCC-2998
HCT-116
HCT-15
HT29
KM12
SW-620
CNS Cancer
SF-268
SF-295
SF-539
SNB-19
SNB-75
Melanoma
LOX IMVI
MALME-3M
M14
MDA-MB-435
SK-MEL-2
SK-MEL-28
SK-MEL-5
UACC-257
UACC-62
Ovarian Cancer
IGROV1
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
NCI/ADR-RES
SK-OV-3
Renal Cancer
786-0
A498
ACHN
CAKI-1
RXF 393
SN12C
TK-10
UO-31
Prostate Cancer
PC-3
DU-145
Breast Cancer
MCF7
MDA-MB-231/ATCC
HS 578T
BT-549
T-47D
MDA-MB-468
MID
Delta
Range


National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC : D - 762257/1
Units :Molar
SSPL :0Y5P
EXP. ID :1112NS71
Report Date :February 07, 2012
Test Date :December 12, 2011
Panel/Cell Line
Leukemia
CCRF-CEM
HL-60(TB)
K-562
MOLT-4
SR
Non-Small Cell Lung Cancer
A549/ATCC
EKVX
HOP-62
HOP-92
NCI-H226
NCI-H23
NCI-H460
NCI-H522
Colon Cancer
COLO 205
HCC-2998
HCT-116
HCT-15
HT29
KM12
SW-620
CNS Cancer
SF-268
SF-295
SF-539
SNB-19
SNB-75
Melanoma
LOX IMVI
MALME-3M
M14
MDA-MB-435
SK-MEL-2
SK-MEL-28
SK-MEL-5
UACC-257
UACC-62
Ovarian Cancer
IGROV1
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
NCI/ADR-RES
SK-OV-3
Renal Cancer
786-0
A498
ACHN
CAKI-1
RXF 393
SN12C
TK-10
UO-31
Prostate Cancer
PC-3
DU-145
Breast Cancer
MCF7
MDA-MB-231/ATCC
HS 578T
BT-549
T-47D
MDA-MB-468
MID
Delta
Range

Continue ……

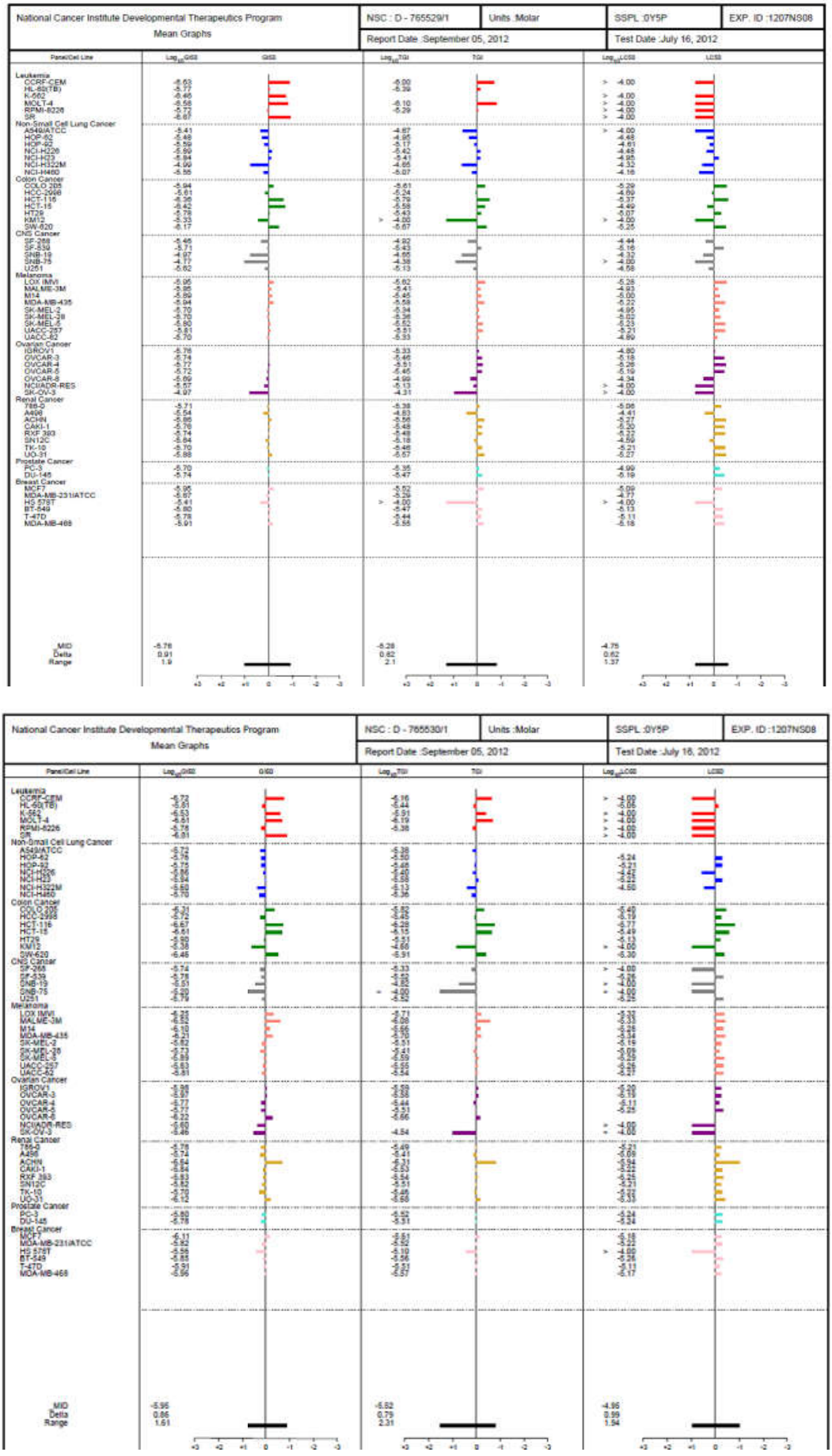


Figure 8. Mean Graphs of the log_{10} values (Molar) of GI_{50}, TGI and LC_{50} of NSC 765529, NSC 765530, NSC 762255 and NSC 762257 obtained from the NCI 60 cell line experiments

Table 1. Chemical structures of compounds 1-7

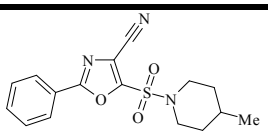
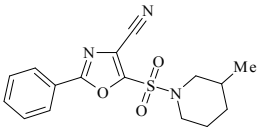
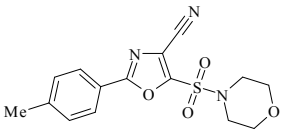
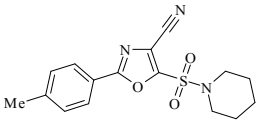
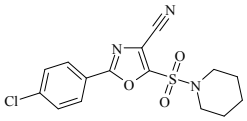
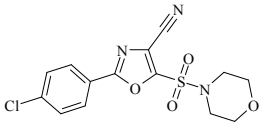
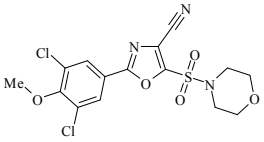
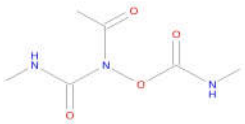
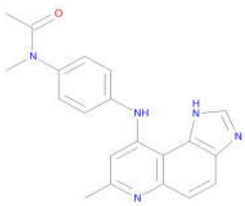
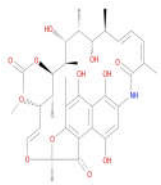
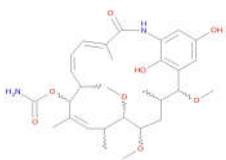
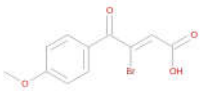
Compound	NCI code NSC	Molecular weight	Chemical structure	Chemical name
1	765529	331.40		5-[(4-methylpiperi-din-1-yl)sulfonyl]-2-phenyl-1,3-oxazole-4-carbonitrile
2	765530	331.40		5-[(3-methylpiperi-din-1-yl)sulfonyl]-2-phenyl-1,3-oxazole-4-carbonitrile
3	762255	333.37		2-(4-methylphe-nyl)-5-(morpholine-4-sulphonyl)-1,3-oxazo-le-4-carbonitrile
4	762256	331.40		2-(4-methylphe-nyl)-5-(piperidine-1-sul-phonyl)-1,3-oxa-zole-4-carbonitrile
5	762257	351.81		2-(4-chlorophe-nyl)-5-(piperidine-1-sulphonyl)-1,3-oxa-zole-4-carbonitrile
6	762258	353.79		2-(4-chlorophe-nyl)-5-(morpholine-4-sulphonyl)-1,3-oxa-zole-4-carbonitrile
7	762259	418.26		2-(3,5-dichloro-4-me-thoxyphenyl)-5-(mor-pholine-4-sulpho-nyl)-1,3-oxazole-4-car-bonitrile

Table 2. Standard Agent LC_{50} COMPARE correlations > 0.65 for NSC 765530 LC_{50} vector (SD = 0.55)

NSC	Name	Structure	Reported Mechanism(s)	HICONC	SD	r
253272	Caracemide			10^{-2} M	0.40	0.69
305884	Acodazole		DNA intercalation (https, 2017; Johnson *et al.*, 2017)	$10^{-3.1}$ M	0.37	0.69
133100	Rifamycin SV		BCL6; prokaryotic (Evans *et al.*, 2014) RNA polymerase (Wehrli *et al.*, 1971)	10^{-3} M	0.39	0.68
330500	Macbecin II		Hsp90? (Martin *et al.*, 2008)	$10^{-3.3}$ M	0.43	0.65
104801	Cytembena			10^{-2} M	0.58	0.65

(r = 0.81), a naphthoquinone analog which is part of the NIH Molecular Libraries program (PubChem substance ID 87335613 (SID, 2017), where it was found to be a 108 nM inhibitor of NSD2. Due to the presence of many quinone compounds, matrix COMPARE was performed with doxorubicin (NSC 123127) and daunorubicin (NSC 82151). NSC 765530 had low, non-zero LC_{50} COMPARE correlations with both doxorubicin and daunorubicin (r = 0.22 and 0.39, respectively). Matrix COMPARE using GI_{50} and TGI vectors did not find improved correlations (GI_{50} = 0.26 and 0.23; TGI = -0.013 and 0.082 for doxorubicin and daunorubicin, respectively). Oxazole is a heterocyclic compound and exhibits a wide variety of anticancer activities (Swellmeen, 2016; Joshi *et al.*, 2016). Among oxazoles it was shown that phorboxazoles display the most cytostatic activity against all 60 cell lines of the National Cancer Institute human cancer test panel with a mean GI_{50} < 0.8 nM (Searle *et al.*, 1995). Thus, these compounds rank among the most potent cytostatic agents discovered. However some new information has not been published to date concerning anticancer activity of these compounds. Differently substituted oxazole moieties have different activity. Indeed the obtained results indicate that compounds NSC 765529 and NSC 765530 showed higher anticancer activity than compounds NSC 762255 and NSC 762257, and compound NSC 765530 exhibited a wide range of anticancer activities.

Conclusion

A series of novel 4-cyano-1,3-oxazole-5-sulfonamides derivatives were synthesized and evaluated for their antitumor activities. The synthesized compounds were subjected to anticancer activity testing. In summary, colon, melanoma, and renal cancer cell lines were particularly sensitive to the compounds NSC 765529, and NSC 765530. The leukemia cell lines SR, CCRF-CEM, MOLT-4 and K-562 showed a significant sensitivity to these compounds with sub-micro molar GI50 values. The compounds NSC 762255, and NSC 762257 showed anticancer activity for the leukemia CCRF-CEM and the non-small cell lung cancer NCI-H522 cell lines also over the range of sub-micro molar GI50 values. We believe that NSC 765529 and NSC 765530 will serve a good lead compounds for further investigation to improve the *in vivo* efficacy of this series as anticancer agents.

Therefore, 4-cyano-1,3-oxazole-5-sulfonamides is structurally novel potent perspective class of anticancer agents suitable for further chemical optimization and structure-activity relationship investigation. These results make the reported oxazole derivatives not only interesting for the further chemical optimization of this class but also for future studies on their mechanism of action and structure-activity relationship. These compounds will be use full to improve the biological effects of oxazoles in a next-generation series. NCI-60 cytotoxicity profiles point toward a possible DNA damage mechanism, due to the similarity with multiple quinone analogs as well as similarity to the profile of acodazole. However, the mechanism is apparently different from that of doxorubicin. Other mechanisms are possible, as rifamycin SV has been shown to inhibit BCL6 (Evans *et al.*, 2014). The sulfone component of these reported compounds is structurally similar to a number of compounds that were found in a BCL6 inhibitor screen (Cerchietti *et al.*, 2010). Additionally, a few possible targets of NSC 40342 (SID, 2017), in particular NSD2, could be an important part of these compounds' cytotoxic effects. Further investigation will be required to uncover relevant mechanisms of action.

Experimental section

General Chemistry Methods. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer in DMSO-d_6 or $CDCl_3$ solution with TMS as an internal standard. IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. The melting points were estimated on a Fisher-Johns instrument.
The chromatomass spectra were recorded on an Agilent 1100 Series high performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MS mass selective detector allowing a fast switching the positive/negative ionization modes. The reaction progress was monitored by the TLC method on Silica gel 60 F_{254} Merck.

Synthetic Procedures. Compounds **3-7** was synthesized as reported earlier (Kornienko *et al.*, 2012). 5-[(4-Methylpiperidin-1-yl)-sulfonyl]-2-phenyl-1,3 -oxazole-4-carbonitrile (1). To a solution of 0.001 mol of 4-cyano-2-phenyl-1,3-oxazole-5-sulfonyl chloride in THF was added 0.0011 mol of 4-methylpiperidine and 0.0011 mol of Et_3N. The mixture was heated for 2 h and kept at 20-25°C for 12 h. The precipitate was filtered off, the solvent was removed in a vacuum. The precipitate was treated whis water, filtered off, dried and recrystallized from EtOH. Yield 74%. Mp 146-148°C. IR (KBr), ν, cm^{-1}: 577, 624, 726, 931, 1053, 1161, 1288, 1332, 1376 (SO_2), 1450, 1550, 1605, 2247 (CN), 2936. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 0.89 (d, 3H, *J*=6.4, CH_3), 1.13-1.22 (m, 2H, piperidine), 1.46 (br s, 1H, piperidine), 1.75 (d, 2H, *J*=12.0, piperidine), 2.95 (t, 2H, *J*=11.6, piperidine), 3.72 (d, 2H, *J*=11.6, piperidine), 7.62-7.72 (m, 3H, Ar), 8.05 (d, *J*=7.2, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$), *δ*: 163.4 (C^{2}_{oxazol}), 151.1 (C^{5}_{oxazol}), 133.1 (C_{Ph}), 129.5 ($2C_{Ph}$), 127.4 ($2C_{Ph}$), 124.4 (C_{Ph}), 117.3 (C^{4}_{oxazol}), 110.8 (CN), 45.6 ($2C_{piperidine}$), 32.8 ($2C_{piperidine}$), 28.8 ($C_{piperidine}$), 21.2 (CH_3). LCMS, *m/z*: 332 $[M+1]^+$. 5-[(3-Methylpiperidin-1-yl)-sulfonyl]-2-phenyl-1,3-oxazole-4-carbonitrile (**2**) were prepared similarly starting from 4-cyano-2-phenyl-1,3-oxazole-5-sulfonyl chloride and 3-methylpiperidine. Yield 71%. Mp 141-143°C (from EtOH). IR (KBr), ν, cm^{-1}: 570, 631, 717, 747, 930, 1007, 1152, 1172, 1329, 1378 (SO_2), 1449, 1477, 1552, 1605, 2248 (CN), 2851, 2923, 2947. ^{1}H NMR (400 MHz, DMSO-d^6), δ: 0.89 (d, *J*=6.4 3H, CH_3), 0.96-1.06 (m, 1H, piperidine), 1.47-1.56 (m, 1H, piperidine), 1.67-1.79 (m, 3H, piperidine), 2.63 (t, 1H, *J*=10.8, piperidine), 2.91-2.96 (m, 1H, piperidine), 3.58-3.68 (m, 2H, piperidine), 7.62-7.73 (m, 3H, Ar), 8.06 (d, *J*=7.6, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$), *δ*: 163.4 (C^{2}_{oxazol}), 151.1 (C^{5}_{oxazol}), 133.1 (C_{Ph}), 129.5 ($2C_{Ph}$), 127.4 ($2C_{Ph}$), 124.4 (C_{Ph}), 117.2 (C^{4}_{oxazol}), 110.8 (CN), 51.7 ($C_{piperidine}$), 45.7 ($C_{piperidine}$), 30.8 ($C_{piperidine}$), 30.2 ($C_{piperidine}$), 24.1 ($C_{piperidine}$), 18.5 (CH_3). LCMS, *m/z*: 332 $[M+1]^+$.

In Vitro Anticancer Screening of the synthesized compounds

One Doses Full NCI 60 Cell Panel Assay. The newly synthesized compounds were submitted to National Cancer Institute NCI, Bethesda, Maryland, U.S.A., under the Developmental Therapeutic Program DTP. The cell line panel engaged a total of 60 different human tumor cell lines derived from nine cancer types, including lung, colon, melanoma,

renal, ovarian, brain, leukemia, breast, and prostate. The target compounds (1-7) were assigned with the following NCI codes NSC 765529, NSC 765530, NSC 762255, NSC 762256, NSC D762257, NSC 762258 and NSC 762259, respectively Primary *in vitro* one dose anticancer screening was initiated, in which the full NCI 60 panel lines were inoculated onto a series of standard 96-well microtiter plates on day 0 at 5000-40,00 cells/well in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine, and then preincubated in absence of drug at 37°C, and 5% CO_2 for 24 h. Test compounds were then added at one concentration of 10^{-5} M in all 60 cell lines, and incubated for a further 48 h at the same incubation conditions . Following this, the media were removed, the cells were fixed *in situ*, washed, and dried. The sulforhodamine B assay is used for cell density determination, based on the measurement of cellular protein content. After an incubation period, cell monolayers are fixed with 10% (wt/vol) trichloroacetic acid and stained for 30 min, after which the excess dye is removed by washing repeatedly with 1% (vol/vol) acetic acid. The bound stain was resolubilized in 10 mM Tris base solution and measured spectrophotometrically on automated microplate readers for OD determination at 510 nm.

Five Doses Full NCI 60 Cell Panel Assay: All the 60 cell lines, representing nine cancer subpanels, were incubated at five different concentrations (0.01, 0.1, 1, 10 and 100 μM) of the tested compounds. The outcomes were used to create $\log_{10}$ concentration *versus* percentage growth inhibition curves and three response parameters (GI_{50}, total growth inhibition (TGI) and LC_{50}) were calculated for each cell line. The GI_{50} value (growth inhibitory activity) corresponds to the concentration of the compound causing 50% decrease in net cell growth. The TGI value (cytostatic activity) is the concentration of the compound resulting in total growth inhibition. The LC_{50} value (cytotoxic activity) is the concentration of the compound causing net 50% loss of initial cells at the end of the incubation period of 48 h. The three dose response parameters GI_{50}, TGI and LC_{50} were calculated for each experimental compound. Data calculations were made according to the method described by the NCI Development Therapeutics Program (https://dtp.cancer.gov/discovery_development/nci-60/default.htm).

The % growth curve is calculated as:
$[(T-T_0)/(C-T_0)]x100$,
where

T_0 is the cell count at day 0,

C is the vehicle control (without drug) cell count (the absorbance of the SRB of the control growth).

T is the cell count at the test concentration at day 3.
The GI_{50} and TGI value are determined as the drug concentration that results in a 50% and 0% growth at 48 hr drug exposure. Growth inhibition of 50 % (GI_{50}) is calculated from:

$[(T-T_0)/(C-T_0)] \times 100 = 50.$

The TGI is the concentration of test drug where:

$100 \times (T - T_0)/(C - T_0) = 0.$

Thus, the TGI signifies a cytostatic effect.

The LC_{50}, which signifies a cytotoxic effect, is calculated as:
$[(T-T_0)/T_0] \times 100 = -50$,
when $T < T_0$.

NCI 60 Cell Panel COMPARE Correlations. COMPARE correlations were performed essentially as described (Boyd *et al.*, 1995). Briefly, vectors of Log GI_{50}, TGI, and LC_{50} concentrations for NSC 765530 were correlated with the set of average GI_{50}, TGI, and LC_{50} vectors, respectively, for the standard agents database (https://dtp.cancer.gov/discovery_development/nci-60/default.htm) or all public NCI-60 vectors, that contained at least 40 overlapping cell lines and had SD > 0.2. LC50 vector correlations were reported for those exceeding 0.6 for the standard agents or 0.7 for the full public synthetic agents database.

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Disclaimer

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